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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,123	08/02/2005	Michel Schneider	BR-033 PUS 01	7493

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,123	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 41-99* is/are pending in the application.

4a) Of the above claim(s) *74 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,41-73 and 76-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/2/05, 11/21/05, 8/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 3/31/2009 is acknowledged. However, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The election of the following species are also acknowledged: perfluorobutane as gas and DPPS as phospholipid.

Status of Claims

Claims 1 and 41-99 are pending, of which claims 73-75 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 41-73 and 76-99 are readable upon the elected invention and are examined herein on the merits for patentability.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-13 of copending Application No. 11/202,008. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods of preparation of a lyophilized matrix which upon contact with an aqueous carrier liquid and a gas, is reconstitutable into a suspension of gas-filled microbubbles stabilized predominantly by a phospholipid comprising a) preparing an aqueous-organic emulsion comprising i) an aqueous medium including water, ii) an organic solvent, iii) an emulsifying composition of amphiphilic materials comprising more than 50% by weight of phospholipid and iv) a lyoprotecting agent; and b) lyophilizing said emulsified mixture. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-39 of copending Application No. 10/584,327. Although the conflicting claims are not

identical, they are not patentably distinct from each other because both sets of claims are drawn to methods comprising preparing an emulsion comprising an organic solvent, a phospholipid and a lyoprotecting agent, and admixing with an aqueous suspension, and freeze-drying to obtain a lyophilized product. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38-42 of copending Application No. 10/584,382. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods comprising preparing an emulsion comprising an organic solvent, a phospholipid and a lyoprotecting agent, and admixing with an aqueous suspension, and freeze-drying to obtain a lyophilized product. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 11/641,289. Although the conflicting claims are not

identical, they are not patentably distinct from each other because both sets of claims are drawn to methods of preparation of a lyophilized matrix which upon contact with an aqueous carrier liquid and a gas, is reconstitutable into a suspension of gas-filled microbubbles stabilized predominantly by a phospholipid comprising a) preparing an aqueous-organic emulsion comprising i) an aqueous medium including water, ii) an organic solvent, iii) an emulsifying composition of amphiphilic materials comprising more than 50% by weight of phospholipid and iv) a lyoprotecting agent; and b) lyophilizing said emulsified mixture. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 41-73 and 76-99 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 11/660,188. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods comprising dispersions of phosphlipids in an aqueous organic emulsion, a lyoprotective agent, and lyophilizing and reconstitution in a pharmaceutically acceptable carrier to provide gas-filled microvesicles Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 41-73 and 76-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dugstad *et al.* (US 6,221,337).

Dugstad discloses microbubble dispersions stabilized by phospholipids predominantly comprising molecules which individually have an overall net charge exhibit advantageous stability, rendering them useful as efficacious contrast agents. An improved process for preparing microbubble-containing contrast agents is also disclosed, this comprising lyophilising an aqueous dispersion of gas microbubbles stabilized by one or more membrane-forming lipids to yield a dried product which may be reconstituted in an injectable carrier liquid to generate a microbubble-containing contrast agent (abstract). According to one embodiment of the invention, a contrast agent for use in the diagnostic studies comprises a suspension of injectable aqueous

carrier liquid of gas microbubbles stabilized by phospholipid-containing amphiphilic material characterized in that said amphiphilic material consists essentially of phospholipid predominantly comprising molecules with net charges. Desirably at least 75% of the phospholipid material bears a net overal charge. Phosphatidylserines represent particularly preferred phospholipids, including dipalmitoylphosphatidylserine, etc. (column 4, lines 9-67). Any biocompatible gas may be entrapped in the microbubbles including air, nitrogen, halogenated hydrocarbon, including perfluorobutane, etc. (column 5, lines 10-67). Contrast agents comprising microbubbles of a perfluoroalkane such as perfluorobutane stabilized by phosphatidylserine are surprisingly stable (column 6, lines 1-12). Microbubbles have an average size of 0.1-10 micron (e.g. 1-7 micron). Contrast agents have a very narrow size distribution (column 6, lines 62+). Since preparation of the contrast agents typically involves a freeze-drying step, it may be advantageous to include a lyoprotective agent such as glycerol, a carbohydrate (e.g. sucrose, mannitol, etc.) or a polyglycol such as polyethylene glycol (column 7, lines 30-45). Contrast agents according to the invention may be prepared by generating a gas microbubble dispersion in an appropriate phospholipid containing aqueous medium and thereafter subjecting the dispersion to lyophilization to yield a dried reconstitutable product (column 7, lines 60+). The process for preparation of the contrast agents includes the following steps i) generating a dispersion of gas microbubbes in an aqueous medium containing a membrane-forming lipid; ii) lyophilizing the thus-obtained lipid-stabilized gas dispersion to yield a dried lipid-containing product and iii) reconstituting said dried product in an injectable liquid carrier.

Step (i) may be effected by subjecting the liquid containing aqueous medium to an emulsion generating technique (e.g. sonication, etc) in the presence of a selected gas. The aqueous medium may further contain enhancers or solubility aids for the lipid such as lipids or alcohols. The gas employed in the emulsification step need not be that desired in the final product. Thus most of this gas may be removed during the subsequent lyophilization step. Emulsification in the presence of a fluorinated alkane such as 4 or 5 carbon atoms may be particularly advantageous in terms of ultimately yielding end products with consistent and narrow size distribution. Emulsification may be done a room temperature or with heating (column 8, line 45 - column 9, line 40). A washing step may be performed (column 9, lines 49-55), as well as size-fractionation (column 10, lines 1-7). See especially Example 1, wherein dispersions of microbubbles stabilized by different phospholipids or phospolipid mixtures were made, including mixtures in water containing 5.4 wt% of a mixture of propylene glycerol and glycerol (it is noted that Dugstad defines glycerol as a lyoprotectant) (3:10) giving a phospholipid concentration of 2-5 mg/ml, the phospholipids being hydrated by ultrasonic treatment and/or heated to 80 C for the stated time. See Table 1. A volume of the solution is distributed in chromatography vials and the head space of each vial is filled with perfluorobutane gas and vials are capped and shaken for 45 seconds. The resulting dispersions were centrifuged, giving microbubbles, washed and lyophilized (column 11-12).

Example 1 differs from the claimed step of "preparing an aqueous-organic emulsion" step comprising i) an aqueous medium including water ii) an organic solvent

substantially immiscible with water iii) an emulsifying composition of amphiphilic material comprising more than 50% by weight of a phospholipid and iv) a lyoprotecting agent," in that preparation of the emulsion does not include specifically include an organic solvent, as recited in instant claim 45. However, Dugstad teaches that the gas employed in the emulsification step need not be that desired in the final product. Thus most of this gas may be removed during the subsequent lyophilization step. Emulsification in the presence of a fluorinated alkane such as 4 or 5 carbon atoms (e.g. which is within the scope of perfluoropentane as claimed in claim 45) may be particularly advantageous in terms of ultimately yielding end products with consistent and narrow size distribution (column 8-9).

One of ordinary skill in the art could have employed perfluoropentane in the emulsification step and would have been motivated to do so since Dugstad specifically teaches that fluorinated alkane such as 4 or 5 carbon atoms may be particularly advantageous in terms of ultimately yielding end products with consistent and narrow size distribution. It is noted that Dugstad does not specifically recite that such would result in an organic-agueous emulsion, however, "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, merely claiming a new use, new function, or new property, which is inherently present in the prior art does not make the

claim patentable. See *In re Best,* 195 USPQ 430, 433 (CCPA 1977), and MPEP § 2112. Regarding claim 46, Dugstad does not specifically recite the amount of perfluoropentane, however, differences in concentration or temperature will generally not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); *In re Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382; or *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Regarding claim 54, the phospholipids would have at least some "targeting" properties, e.g. would associate with lipids. Regarding claim 55, 58 and 61, PEG modified phospholipids are disclosed (column 3, line 36). Regarding claims 70-73, Dugstad does not specifically recite D_n and D_{v50}, however, Regarding the claimed D_{v50}/D_n ratio, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 1, 41-73 and 76-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (WO 98/04074).

Unger discloses in Example 9 lipid aggregates including hydration of dry lipids by heating and stirring (70 % DMPC / 20% DMPA / 10% DMPE-PEG5000), heating at 45-50 C, and sonication. Perfluorohexane was added to the mixture and the mixture was agitated. Particle size is from 0.5 to 10 microns to an entire population of particles under 2 microns. Micrometer filtration is disclosed. In Example 10, lipid aggregates of nanometer size are formed according to Example 9, except that 1-bromoperfluorobutane is added to the lipid mixture before the heating and sonication step. The aggregates are lyophilized which results in porous solid structtues. The structures may be stored under a head space of an insoluble gas such as perfluoropropane or sulfur hexafluoride to produce porous gas-filled particles.

Examples 9 and 10 of Unger differ from the claims in that a lyoprotective agent is not included, and Unger does not specifically recite that sonication of perfluorohexane or bromoperfluorobutane results in an organic aqueus emulsion.

It would have been obvious to one of ordinary skill in the art to include a lyoprotective agent in the mixture prior to lyophlization because Unger specifically teaches that it is advantageous to include a lyoprotectant such as sorbitol, mannitol, etc. (page 51), and that lyophilization has benefits such as extended shelf life. While Unger does not specifically recite that sonication of aqueous solution of phospholipid and perfluorohexane or bromofluorobutane results in an aqueous organic emulsion, it is noted that such components are listed by Applicant as organic solvents, however,

"Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, merely claiming a new use, new function, or new property, which is inherently present in the prior art does not make the claim patentable. See *In re Best,* 195 USPQ 430, 433 (CCPA 1977), and MPEP § 2112. Regarding claim 46, Unger does not specifically recite the amount of organic component, however, differences in concentration or temperature will generally not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); *In re Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382; or *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Regarding claim 54, Unger recited targeting agents (page 10, lines 8-16). Regarding claim 55, 58 and 61, PEG modified phospholipids are disclosed (column 3, line 36). Regarding claims 70-73, Unger does not specifically recite D_n and D_{v50}, however, Regarding the claimed D_{v50}/D_n ratio, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the

burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS